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Akzeptierter Artikel

Titel: The Directed Metalation Group Dance. Regioselective Iterative Functionalization of 7-Azaindole by Controlled Annular Isomerism

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Zitierweise: *Angew. Chem. Int. Ed.* 10.1002/anie.201901724
Angew. Chem. 10.1002/ange.201901724

Link zur VoR: http://dx.doi.org/10.1002/anie.201901724
http://dx.doi.org/10.1002/ange.201901724

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The Directed Metalation Group Dance. Regioselective Iterative Functionalization of 7-Azaindole by Controlled Annular Isomerism

Michael E. Dalziel[a], Jignesh J. Patel[a], Meagan K. Kaye[a], Jennifer L. Cosman[a], Matthew O. Kitching*[b], Victor Snieckus*[a]

Ted Taylor In Memoriam, a man for all heterocycles

Abstract: The regioselective functionalization of 7-azaindole by controlled annular directed metalation group isomerism is reported. The N-7 carbamoyl azaindoles **2a–b** undergo regioselective metalation and electrophile quench to furnish C-6 substituted derivatives **3** which, in the presence of catalytic amount of $ClCONR_2$ afford products **4** by an N-7 to N-1 carbamoyl group dance. A second directed metalation-electrophile quench sequence leads to 2,6-substituted azaindoles **5**. Optimization of metalation conditions for C-2 and C-6, separately and iteratively, is presented. Using the directed metalation group dance strategy, a late-stage deuteration of an antipsychotic drug is described. Overall, the controlled annular isomerism of a carbamoyl directing group allows multiple functionalization events of the bioactive azaindole scaffold.

Azaindoles occupy a prominent position in drug discovery research due to their diverse bioactivities, especially in the area of protein kinase inhibition for the development of anti-cancer therapies. Among the four isosteres, the 7-azindole scaffold, also present in a rare class of natural products,[1] has emerged as the key heterocycle for structural modification for provision of new bioactive molecules (**Figure 1, A**).[2] Among the synthetic routes for 7-azaindoles, metalation-based methodologies have achieved dominance over classical processes due to advantages of regioselectivity, multiple substitution and ready modification of the prototype nucleus.[3,4] In previous efforts, we have demonstrated the power of the directed *ortho* metalation (DoM) reaction in new halogen dance strategies,[5] anionic *ortho*-Fries rearrangement processes,[6] latent directed metalation group (DMG) protocols,[7] and, as demonstrated on the 7-azaindole framework, "walk-around-the-ring" sequences.[4a,4b,8] Whilst synthetically powerful, these metalation based approaches involve several steps: DMG introduction, its use to direct the functionalization event, and its subsequent removal or modification.

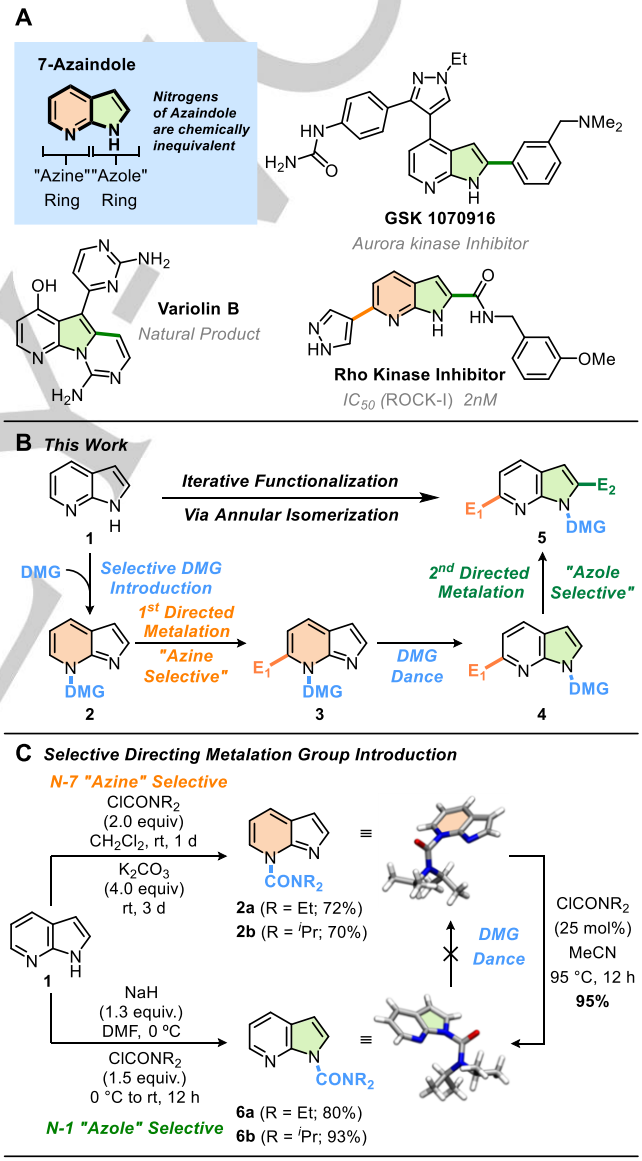

Figure 1. A) 7-Azaindole in natural and bioactive molecules and drugs with azine and azole ring functionalization. B) Selective iterative functionalization through DMG controlled annular isomerization. C) Regioselective introduction and migration studies on 7-azaindole.

Inspired by the work of Sames on silyl migration,[9] we hypothesized that the N-7 DMG azaindoles **2** would undergo DoM-mediated C-6 functionalization (**Figure 1, B**) and, by azine to azole ring DMG dance to the thermodynamically more stable

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isomer (**3→4**), would allow C-2 functionalization to afford 2,6-disubstituted azaindoles **5**. Such a migration sequence

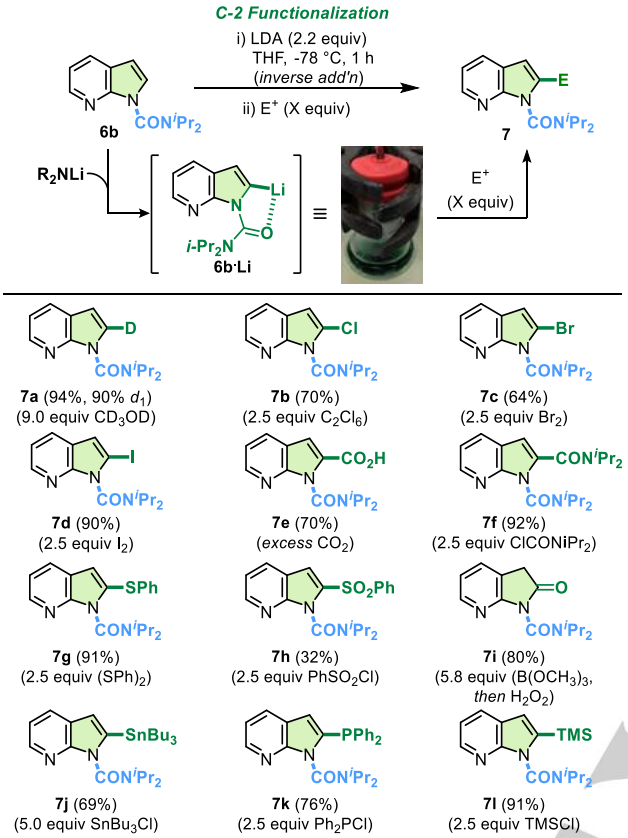

Figure 2. Regioselective synthesis of C-2 substituted 7-azaindoles. Reactions were performed on a 0.41 mmol scale. Reaction conditions: **6b** (0.41 mmol, 1.0 equiv), LDA (0.90 mmol, 2.2 equiv), THF (0.10 M), –78 °C, 1 h; then E^+ (1.0–3.7 mmol, 2.5–9.0 equiv), –78 °C (1 h) to 23 °C (12 h). Yields of isolated products.

circumvents the removal and introduction of the DMG and would allow the same group to direct functionalization at a new, remote location. In continuing efforts to invent new DoM-founded chemistry,[10] we now report the successful attainment of the DMG dance concept (**3→4**), which establishes a regioselective route to 7-azaindoles bearing diverse C-2 (**Table 1**) and C-2 and C-6 (**Figure 3**) substitution patterns.

In order to test the DMG dance concept, the regioisomeric N-7 (**2a,b**) and N-1 (**6a,b**) carbamoyl azaindoles were prepared (**Figure 1, C,** for optimization see SI).[11] The choice of the $CONR_2$ as DMG was dictated by its previous efficacy in DoM chemistry.[4b,12] Although N-1 DMG 7-azaindoles have been synthesized previously,[4b,13] to the best of our knowledge, N-7 DMG-bearing 7-azaindole isomers are unknown. The identity of the two isomers was unambiguously confirmed by X-ray crystallography. To assess the expected thermodynamically driven DMG dance, compound **2b** was subjected to a catalytic quantity of di-isopropyl carbamoyl chloride which led, under optimized conditions (see SI, Table 1), to the isomeric derivative **6b** in 95% yield.

With conditions for the introduction and migration of the DMG in place, selective functionalization of each ring in the azaindole scaffold was undertaken. Firstly, the DoM route to 2-substituted 7-azaindoles **7** was investigated (**Figure 2**). After considerable optimization (see SI), treatment of **6b** with LDA using an inverse addition protocol led to efficient C-2 metalation affording **7a** (90% d_1 by ^{1}H NMR). A comprehensive study of the reaction scope was undertaken, leading to the preparation of a variety of carbon, halogen, sulfur, and phosphorus 2-substituted derivatives **7b–l**. Of particular note is the oxidative conversion of the $B(OR)_2$ derivative into the azaoxindole **7i**[14] and the availability of substrates for further useful metalation (**7e**, **f**, **h**, **j**) and cross-coupling (**7b–d, g, i, j, l)** chemistry.

With conditions for C-2 functionalization in hand, investigation of the C-6 metalation process was conducted (**Table 1, A**). Metalation of **2a** using *s*-BuLi/TMEDA or LDA followed by CD_3OD quench resulted in product with undetectable *d*-incorporation, suggesting lower C-6 H acidity compared to that of the pyridine C-2 acidity.[15] Using Barbier conditions (LDA/TMSCl)[16] led to quantitative conversion to **3** (E = TMS) by GC-MS analysis of crude product (entry 4) but normal aqueous work-up resulted in desilylation to starting material **2a**. Switching to anhydrous work-up conditions resulted in formation of products **3** (E = TMS and Bpin) in excellent conversion by ^{1}H NMR (entries 5 and 6) but subjection to normal work-up also resulted in isolation of starting material **2a**, undoubtedly the result of *ipso*-protodesilylation and *ipso*-protodeboronation.[17] In view of the limited electrophile-base compatible combinations for the Barbier and Martin procedures, we returned to examine C-6 metalation of **2b** using inverse addition-electrophile quench procedures. Gratifyingly, 2.5 equiv of LDA under inverse addition conditions gave product **3a** with modest *d*-incorporation (entry 7, 73% d_1). Switching to the more sterically hindered LiTMP and modification of reaction temperature improved the level of anion formation considerably (entries 8 and 9, 90% and 93% d_1, respectively).

Under the optimized conditions, the C-6 DoM chemistry of **2b** was generalized (**Table 1, B**). As shown, the methodology allows the synthesis of halogen containing **3b–d**, carbon-based **3e–g**, and heteroatom-based **3h** azaindole derivatives. A potentially useful finding is the observation of controlled mono-/bis-iodination of **2b** simply by modification of the I_2 stoichiometry (**3c** *vs* **3d**). Although high levels of conversion (>92%) were observed in all cases (^{1}H NMR analysis), yields of isolated products were compromised due to their instability to column chromatography. Fortunately, simple exposure of the crude reaction products to the optimized DMG dance conditions afforded 6-substituted azaindoles **4** which proved readily separable. In this manner, methyl, carbamoyl, carbinol, and sulfide substituted products **4a–h** (**Table 1, C**) were readily accessible in good to excellent yields.

To fully establish the DMG dance strategy for general regioselective C-2 and C-6 functionalization of the 7-azaindole scaffold, C-2 DoM reactions of substrate **4** were undertaken. Application of the optimized C-2 metalation conditions on **4**, followed by electrophile quench, afforded products

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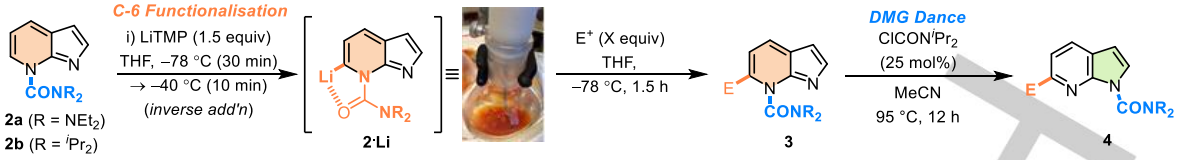

A Optimization of *C*-6 metalation

Entry[a,b]	Addition Order	Base (equiv)	Electrophile	Conv[c]
1	Normal	s-Buli/TMEDA (1.2/1.3)	CD_3OD	0
2	Normal	LDA (1.3)	CD_3OD	0
3	Normal	LDA (2.5)	CD_3OD	0
4[d]	Barbier	LDA (1.5)	TMSCl	0
5[e]	Barbier	LDA (1.5)	TMSCl	91
6[e]	Barbier	LDA (2.5)	iPrOBPin	85
7[d]	Inverse	LDA (2.5)	CD_3OD	73
8[d,f]	Inverse	LiTMP (2.5)	CD_3OD	90
9[d,f]	Inverse	LiTMP (1.5)[e]	D_2O	93

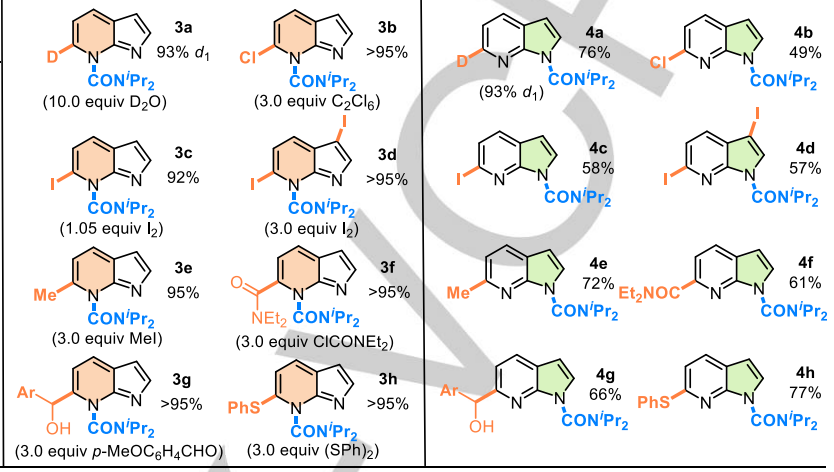

Table 1. Optimization of C-6 metalation, substrate scope and DMG migration from N-7 to N-1. A: [a] All reactions were performed on a 0.41 mmol scale. [b] Entries 1–6: **2a** as starting material; entries 7–9: **2b** as starting material. [c] % deuteration / conversion was determined by 400 MHz ^{1}H NMR analysis on the crude reaction mixture. [d] Aqueous workup. [e] Anhydrous work up. [f] The reaction was stirred at –78 °C for 30 mins before being warmed to –40 °C for 10 min. Electrophile was added at –78 °C, and the reaction was stirred for 1.5 h at this temperature. [g] LiTMP was prepared using 1.6 equiv 2,2,6,6-tetramethylpiperidine and 1.5 equiv t-BuLi in THF solution. B: [h] Reaction conditions: **2b** (0.41 mmol, 1.0 equiv), LiTMP (0.62 mmol, 1.5 equiv), THF (0.10 M), –78 °C (30 min) to –40 °C (10 min); then E+ (0.43–4.1 mmol, 1.05–10.0 equiv), –78 °C, 1.5 h. [i] All % yields represent conversion as determined by 400 MHz ^{1}H NMR on the crude reaction mixture. C: [j] Reaction conditions: **2b** (0.41 mmol, 1.0 equiv), LiTMP (0.62 mmol, 1.5 equiv), THF (0.10 M), –78 °C (30 min) to –40 °C (10 min); then E+ (0.43–4.1 mmol, 1.05–10.0 equiv), –78 °C, 1.5 h. After subsequent work-up: **3** (assumed 0.41 mmol, 1.0 equiv), ClCONiPr$_2$ (0.10 mmol, 25 mol%), MeCN (0.04 M), 95 °C, 12 h. [k] All % yields are of isolated products over the two steps (i.e. from **2b**)

5a–j in good yields (67–89%) (**Figure 3**). Of particular note, the presence of the powerful N-1 DMG overrides any competitive metalation at C-5 aided by the potential DMGs present at C-6 (**5j**,**k**) including the powerful amide directing groups (**5l**). Given the prevalence of bioactive 2-arylated 7-azaindole variants (e.g. GSK 1070916, **Figure 1, A**), we explored the feasibility of the cross-coupling of **5j** with 4-nitrophenylboronic acid, two expectedly proficient coupling partners.[18] In a preliminary encouraging study, Suzuki-Miyaura coupling resulted in the formation of product **8** in good yield.

In consideration of the interest in deuterated molecules as new drug entities,[19] we undertook a deuteration study of the antipsychotic agent L-745870 (**9, Figure 4**). Thus, compound **10**, prepared (see SI) and subjected to deuteration using the standard LDA protocol afforded **12** (88% yield, 74% d_1). Subjecting the isomeric N-7 carbamoyl derivative **11** to the LiTMP/D_2O conditions as previously optimized (**Table 1, A**) followed by the catalytic DMG dance procedure afforded deuterated material **13** in 37% yield over two steps (79% d_1).

In summary, we have demonstrated a new DMG dance concept and developed it for a general and highly regioselective synthesis of 2- and 6- and combined 2,6-substituted 7-azaindole derivatives. In addition, we have illustrated an application of this annular DMG isomerism concept in the regioselective synthesis of deuterated antipsychotic agent L-745870, a result which may anticipate late-stage derivatization of other commercial drugs.

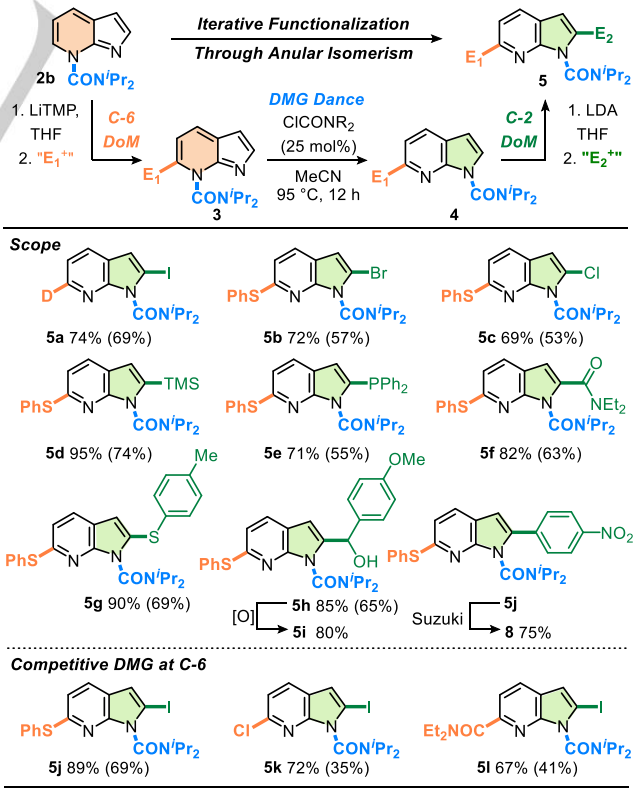

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Figure 3. Iterative C-6 and C-2 functionalization of 7-azaindole by DoM and DMG dance reactions. [a] yield from **4.** [b] Yield from **2b** given in brackets over three step sequence. For **5h**→**5i** (Oxidation), **5j**→**8** (Suzuki coupling), see SI.

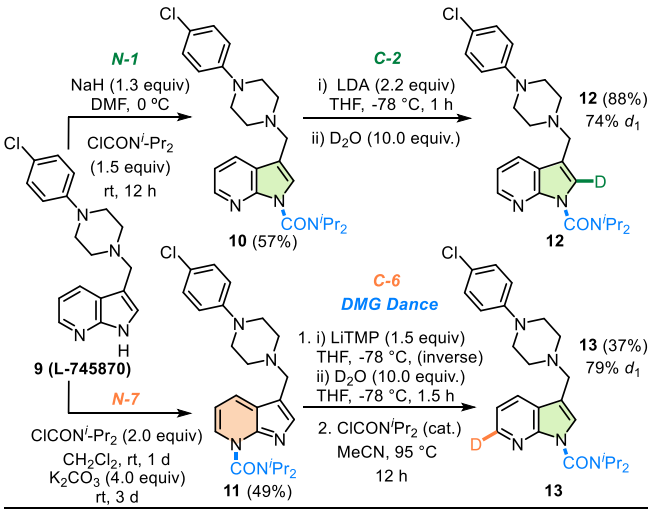

Figure 4. Regioselective deuteration of antipsychotic agent L-745870.

Aside from the viability of the DMG dance methodology for the construction of new and difficult to access 7-azaindoles, its adaption to similarly two-nitrogen related aza-heterocycles may be envisaged. Pertinent work is in progress and will be reported in due course.

Acknowledgements

NSERC Canada is warmly acknowledged for consistent support via the Discovery Grant (DG) program (VS) as is the Royal Society for a University Research Fellowship (MOK). We thank Dr. Francoise Sauriol for expert NMR assistance, Dr. Gabriele Schatte for X-ray analysis and Adrian Bailey for DFT calculations.

Keywords: Azaindole • DMG Dance • Iterative metalation • Regioselectivity • Lithiation

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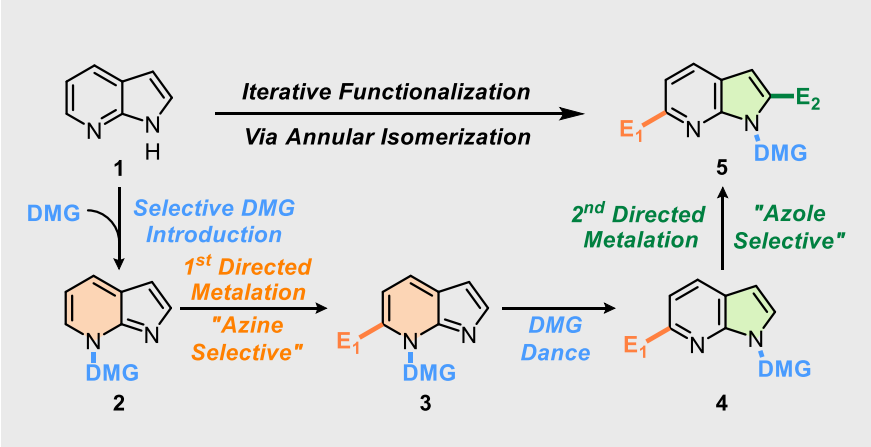

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The Directed Metalation Group Dance. Regioselective Iterative Functionalization of 7-Azaindole by Controlled Annular Isomerism

The Directed Metalation Group Dance

A new Directed Metalation Group (DMG) dance concept is disclosed on the 7-azaindole framework. Azine selective (N-7) incorporation of the carbamoyl DMG allows C-6 functionalization via directed *ortho* metalation. The controlled annular DMG dance N-7 to N-1 generates the azole (N-1) DMG derivative. Second and iterative DoM reactions allow the synthesis of 2,6-substituted azaindoles in good yields. The DMG dance methodology is demonstrated in site selective deuteration of a drug scaffold.